EXHIBIT D

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Appeal No. 00-1260

United States Court of Appeals

for the

Federal Circuit

BIOVAIL CORPORATION INTERNATIONAL,
BIOVAIL LABORATORIES, INC., and GALEPHAR P.R., INC. LTD.,

Plaintiffs-Appellants,

– v. –

ANDRX PHARMACEUTICALS, INC.,

Defendant-Appellee.

APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF FLORIDA IN 98-CV-7096,
JUDGE WILLIAM P. DIMITROULEAS

BRIEF OF PLAINTIFFS-APPELLANTS BIOVAIL CORPORATION INTERNATIONAL, BIOVAIL LABORATORIES, INC., and GALEPHAR P.R., INC. LTD.

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MAY 22, 2000

CERTIFICATE OF INTEREST

Pursuant to FED. CIR. R. 47.4, counsel for Appellants Biovail Corporation International, Biovail Laboratories, Inc., and Galephar P.R., Inc., Ltd., certifies the following:

1. The full name of every party or amicus represented by me is:

Biovail Corporation International,

Biovail Laboratories, Inc., and

Galephar P.R., Inc., Ltd.

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is:

Plaintiffs-Appellants are the real parties in interest.

3. All parent corporations and any publicly traded companies that own 10% or more of the stock of the party or amicus curiea represented by me are:

Biovail Corporation International has no parent corporations and no publicly traded corporations own 10% or more of its stock. Biovail Laboratories Inc. is a wholly owned subsidiary of Biovail Corporation International. Galephar P.R., Ltd., is a private corporation which has no parent corporations, and no publicly traded company owns 10% or more of its stock.

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court are:

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3/22/2000
Date

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Pursuant to FED. CIR. R. 47.5, counsel states that no other appeal in or from this same civil action or proceeding in the lower court or body was previously before this or any other court of appeals. Counsel knows of no case pending in this or any other court that will directly affect or be directly affected by the outcome of this Court's decision in this appeal.

JURISDICTIONAL STATEMENT

This case, No. 98-7096-CIV in the Southern District of Florida, was a civil action, under 35 U.S.C. § 281 (1994) for patent infringement as defined in 35 U.S.C. § 271(e) (1994). A43–46. The district court's jurisdiction over this civil action was based in part on 28 U.S.C. § 1338 (1994), as a claim arising under an act of Congress relating to patents. *See* A44. The district court entered final Judgment on March 6, 2000. A1. Plaintiff-Appellants Biovail Corporation International, Biovail Laboratories, Inc., and Galephar P.R., Inc., Ltd., timely filed their Notice of Appeal from that Judgement, and invoke the jurisdiction of this Court of Appeals under 28 U.S.C. § 1295(a)(1) (1994).

STATEMENT OF ISSUES

1. Whether the trial court erred as a matter of law in its claim construction:

(a) by limiting the claim covering an extended release drug formulation to the drug only as manufactured, before it is ingested;

(b) by rejecting the patentees' definition of the term "wetting agent" set forth in a Markush group in the claim itself; and

(c) by adding an extraneous limitation requiring that the claimed composition admixture be "homogenous".

2. Whether the trial court clearly erred in finding that the ANDA applicant's product does not form an admixture in the body when ***all*** evidence, including the applicant's own experts, proved that it does.

3. Whether the trial court erred in concluding that the scope of the prior art and statements made during the prosecution preclude a scope of protection under the doctrine of equivalents that would include an admixture formed in the body.

STATEMENT OF THE CASE

Galephar P.R., Inc., Ltd., ("Galephar") is the owner, and Biovail Corporation International and Biovail Laboratories, Inc., (collectively "Biovail") are the exclusive licensees of U.S. Patent No. 5,529,791 ("the '791 patent"), entitled, "Extended Release form of Diltiazem." A2337; A3179–87.

Biovail is a pharmaceutical product development company specializing in advanced oral controlled release delivery technologies. A2336. Since obtaining approval from the FDA in September 1995, Biovail has marketed an extended release form of Diltiazem under the trade name Tiazac®. A2337. The FDA lists Tiazac® and the '791 patent in its book of *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "*Orange Book*") under its active ingredient, Diltiazem hydrochloride. A2337.

On June 22, 1998, defendant-appellee Andrx Pharmaceuticals, Inc. ("Andrx") filed an Abbreviated New Drug Application ("ANDA") with the FDA under the Federal Food, Drug, and Cosmetic Act § 505(j), 21 U.S.C. § 355(j) (1994), asking the FDA to approve a proposed generic equivalent to Tiazac®. A2337. Andrx filed paragraph IV certifications under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (1994) and 21 C.F.R. § 314.95 (1998), denying that its ANDA product infringed the '791 patent and asserting that the '791 patent is invalid. A2338. Biovail received notice of Andrx's application and certification on

August 25, 1998. A2338. Biovail and Galephar timely commenced this civil action for patent infringement under 35 U.S.C. §271(e)(2)(A)(1) on October 7, 1998. A43–47.

No party requested a jury trial. The court held a bench trial on January 24 and 31, and February 14–16, 2000. A3036; A3048; A3097; A3139, A3167. Before the trial began, the parties filed proposed findings of fact and conclusions of law. The district court mechanically adopted parts of Andrx's proposed findings of fact and conclusions of law (submitted before any evidence was even offered) almost verbatim as its own findings and conclusions under FED. R. CIV. PROC. 52, *Compare* A2–24 *with* A2420–95. The district court concluded that the claims of the '791 patent could not be construed to cover post-ingestion infringement. Biovail filed this appeal from the district court's final Judgment, entered March 6, 2000. A1.

STATEMENT OF FACTS

The Formulation Claimed In The '791 Patent

The '791 patent is directed to an extended-release formulation of Diltiazem, a drug used to treat hypertension and angina. A3; A3183. Although Diltiazem is insoluble at the main pH of the body, salts of Diltiazem, such as Diltiazem hydrochloride, are soluble. A3064–65. Thus, various prior art formulations used the soluble Diltiazem hydrochloride form of the drug. *E.g.*, A14916; A14927; A14935.

Diltiazem hydrochloride is soluble in the stomach, which is very acidic. A3065. In the intestine, however, where the pH is less acidic, some of the Diltiazem hydrochloride reverts to Diltiazem, and is much less soluble. A3065.

The formulation of the '791 patent consists of a microcapsule, designed to maintain the solubility of Diltiazem. Each of the microcapsules consists of a "bead," encapsulated by a microporous membrane. The microporous membrane includes a water-soluble or water-dispersible polymer or copolymer, and a water-, acid- and base-insoluble polymer and a pharmaceutically-acceptable adjuvant. A3183–87.

Each "bead" contains a pharmaceutically acceptable salt of Diltiazem, such as Diltiazem hydrochloride, in admixture with an effective amount of a "wetting agent." *Id.*. The "wetting agent" is defined, both in the '791 patent and in a Mar-

kush group in claim 1 of the patent to include "sugars." A3183 (col. 3); A3186–87. The purpose of the admixture is "to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein." A3186–87. The net result, as shown by clinical tests described in the '791 patent, and the contribution to the art made by this invention, is that the combination covered by the claim results in a formulation that may be administered once-a-day and that the plasma concentration variations of the drug are lower than those obtained with prior art products given twice a day. A3186.

Claim 1 is the only independent claim of the '791 patent:

> 1. [a] An extended-release galenical composition of one or more pharmaceutically-acceptable salts of Diltiazem which comprises
>
> [b] beads containing an effective amount of one or more of said Diltiazem salts as the active ingredient,
>
> [c] each bead containing one or more of the Diltiazem salts and an effective amount of a wetting agent in admixture with the one or more Diltiazem salts to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein,
>
> [d] said beads being coated with a microporous membrane comprising at least a water-soluble or water-dispersible polymer or copolymer, and a water-, acid- and base-insoluble polymer and a pharmaceutically-acceptable adjuvant, and
>
> [e] wherein the wetting agent is selected from the group consisting of sugars, C_{12}-C_{20} fatty acid esters of sucrose or xylose, glycerides of sucrose, fatty acid esters of polyoxyethyl-

> ene, ethers of fatty alcohols and polyoxyethylene, esters of sorbitan, esters of polyoxyethylene sorbitan, alcohol-polyglycide esters, glyceride-polyglycides, lecithins and a combination thereof.

A3186–87 (formatting and reference letters added).

Andrx's ANDA Product

Biovail markets Tiazac®, a once-a-day extended release form of Diltiazem covered by claim 1 of the '791 patent. A2329–30. Biovail's Tiazac® product was approved by the Food and Drug Administration ("FDA") in 1995, and Biovail's '791 patent is listed in the FDA's "Orange Book" as covering Tiazac®. *Id.*

Biovail's infringement claim arises out of an ANDA filed by Andrx to market a generic form of Tiazac®. Andrx asserts that its ANDA product is bio-equivalent to Biovail's Tiazac® product, A3442, an assertion accepted for purposes of this proceeding only.

Like Tiazac®, Andrx's ANDA product is a microcapsule that includes a microporous membrane encapsulating a bead. A3069. The microporous membrane of Andrx's ANDA product is virtually identical to the membrane disclosed in Example 4 of the '791 patent. A15635. Andrx tried to use different membranes when it developed its ANDA product, but their alternatives proved "unacceptable" — the only membrane that worked was the membrane from Example 4 of the '791 patent. A15635.

The Andrx bead includes Diltiazem hydrochloride and sugar (which claim element [e] defines as a wetting agent, A3183.), but they are not admixed in the product during manufacture. A11–12. Instead, the Andrx bead has a sugar/starch core, surrounded by a mixture of Diltiazem hydrochloride, ethylcellulose, and polyvinylpyrrolidone (PVP). A9–10.

Thus, Andrx argued that its ANDA product, as manufactured, did not infringe claim 1 of the '791 patent because it does not contain an "admixture" of Diltiazem hydrochloride and sugar.

Biovail's Proof of Post-Ingestion Infringement

As to the issue of infringement, it was indisputable that Andrx's ANDA product literally meets elements [a], [b], [d] and [e] of claim 1. A12684; A12787; A3145; A3066–67; A3185–86.

Thus, the infringement issue that was tried was whether Andrx's ANDA product met claim element [c], i.e., whether it had "an effective amount of a wetting agent in admixture with the one or more Diltiazem salts to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein." A3186–87.

Andrx moved for summary judgment of non-infringement on the theory that Diltiazem hydrochloride and sugar were not "admixed" in the bead of

Andrx's ANDA product. A2744. In response, Biovail explained that infringement would occur ***after*** Andrx's ANDA product was ingested, because water would permeate the microporous membrane in the gastrointestinal tract and dissolve the sugar, which then admixes with the with the Diltiazem hydrochloride. A2744. Andrx filed a second summary judgment motion contending that if claim 1 of the '791 patent was construed to cover post-ingestion infringement, it was invalid in view of the prior art. A2744.

In an order issued January 6, 2000, the district court denied both motions. A 2742–52. The district court recognized that construction of claim 1 was a legal issue, and held:

> [T]here is nothing in the claim that limits the claimed compound to the pre-ingestion form. Rather, the claim in the '791 patent specifically mentions how the compound performs after ingestion. Thus, if Andrx's product forms the claimed admixture in the stomach, it could infringe the Biovail patent.

A2747–48. The district court also denied the motion for summary judgment of invalidity. A 2751–52.

At trial, Biovail introduced the expert testimony of Dr. Robert Langer and Dr. Edith Mathiowitz. Dr. Langer is the Germeshausen Professor of Chemical and Biomedical Engineering at the Massachusetts Institute of Technology, and an expert in the field of drug delivery systems. A3063–64; A13369–452. Dr. Mathiowitz is an Associate Professor of Medical Science and Engineering at

Brown University, who conducts research in the general field of drug delivery systems. A3049.

Dr. Mathiowitz conducted several experiments. She first observed that Andrx's microcapsules became soft after they were immersed in solution. A3049. Dr. Mathiowitz then immersed Andrx's microcapsules in a solution and weighed them at various time intervals to measure the amount of weight that they lost over time. This "weight loss study" demonstrated that something other than Diltiazem leaves the microcapsules at various time intervals (1, 2, 3, 4, 6, 8, 10, 12, 16, and 20 hours). A3069–72; A13453; A13467; A14799–800; A14807; A14822; A14834.

Dr. Mathiowitz prepared scanning electron micrographs ("SEM's") in accordance with well-established scientific procedures. A3050; A3053–54; A14780; A14804. The SEM's show that sucrose leaves the sugar/starch seed at various intervals. A3053–54. These SEM's graphically illustrate the dissolution of the sucrose in the sugar starch seed by comparing the bead before immersion (A13610), after 20 minutes (A13620), after 30 minutes (A13623), after 45 minutes (A13625), after one hour (A13629), after 3 hours (A13647), and after 8 hours (A13638).

Finally, Dr. Mathiowitz conducted glucose tests of the solution in which the Andrx microcapsules had been immersed for the weight loss studies, and con-

firmed from the presence of glucose that sucrose comes out of the beads. A3050; A3052–53; A13463. Dr. Mathiowitz used a very small amount of sodium azide to inhibit bacterial growth, but it had no effect on the results. A3055.

Based on the foregoing experiments, Dr. Langer testified that after the Andrx ANDA product has been ingested, water penetrates the membrane of the microcapsules, penetrates to the sugar starch core, dissolves the sugar, and the sugar forms an admixture with Diltiazem hydrochloride within the membrane. A3069–70. Indeed, the dissolution of the sucrose from the sugar/starch core is dramatically visible in the SEM's, which show that the sugar/starch core begins to disintegrate within minutes of being immersed. *Compare* the bead before immersion (A13610), after 20 minutes (A13620), after 30 minutes (A13623), after 45 minutes (A13625), after one hour (A13629), after 3 hours (A13647), and after 8 hours (A13638).

Dr. Langer also testified that the bioavailability studies from Andrx's ANDA demonstrate that the admixture of sugar and Diltiazem hydrochloride in the Andrx bead maintains the solubility of Diltiazem in each bead so that it is unaffected by the pH of the gastrointestinal tract or other adverse conditions. A3070–71; A3516; A6287.

Andrx's Non-Infringement Theories

Andrx called Dr. Norman Weiner, a pharmacy professor from the University of Michigan, as an expert on surface chemistry. A3127. He admitted that there will be "mixing" of sucrose and Diltiazem hydrochloride in the bead of the Andrx ANDA product in the gastrointestinal tract.

> Q. Do you have any doubt that in the Andrx product when liquid reaches the sugar core, that sugar then mixes in with the Diltiazem while it's still in the membrane?
> A. That is almost certainly true, but not as a homogeneous mixture.

A3145. Andrx also offered the testimony of Dr. Umesh Banakar, a consultant with a Ph.D. in pharmaceutical technology. A3103. Both Dr. Banakar and Dr. Weiner criticized the tests conducted by Dr. Mathiowitz on the Andrx ANDA product, but neither conducted any tests of their own.

Dr. Banakar attempted to equate Andrx's formulation with a prior art formulation disclosed in U.S. Patent No. 4,960,596 to Debregeas ("the Debregeas '596 patent"). A14935–51; A3125–26. The Debregeas '596 patent, however, discloses a formulation in which a sugar/starch seed is coated with alternating layers of Diltiazem hydrochloride and polyvinylpyrrolidone ("PVP"), and then coated with a membrane that includes shellac as a major component. A14935 (Col. 3, lines 10–17; 49–55). In contrast, the Andrx formulation uses the membrane disclosed in Example 4 of the '791 patent. A3066–67. Shellac is a low

molecular weight compound that is 95% resin, so its classification as a polymer is dubious. A3072; A3076; A3122; A14975. Dr. Banakar admitted that shellac is an enteric coating that does not dissolve in the stomach and that shellac controls the release rate of Diltiazem in the Debregeas formulation. A3108; A3115–16. For this reason, the Debregeas shellac membrane will not enable the sucrose in the sugar/starch seed to form an admixture with the Diltiazem "to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein," as is required in claim element 1[c]. A3082. Significantly, neither Dr. Banakar nor Dr. Weiner conducted any experiments on the Debregeas formulation to determine whether an admixture of Diltiazem and sugar would form after it was ingested.

The Debregeas '596 patent was cited during the prosecution of the grandparent application for the '791 patent. The inventors explained to the examiner that even though Debregeas disclosed a sugar (saccharose)/starch seed upon which Diltiazem was layered, the saccharose in the central core of the Debregeas bead "***cannot*** act as a wetting agent" even after the Debregeas formulation was ingested "because in order to do so the saccharose must be ***mixed*** with the Diltiazem and, therefore saccharose must be ***in solution with Diltiazem.*** Unfortunately in this system saccharose can only end up ***in solution*** after all the layers of Diltia-

zem are dissolved." A14507; A14521 (emphasis added). Neither Dr. Banakar nor Dr. Weiner disagreed with this explanation.

Dr. Weiner testified, based on his general knowledge of surfactants, that he expected sugar in solution would not be a wetting agent for Diltiazem. A3135. However Dr. Weiner is not an expert on Diltiazem; indeed, he admits he has no prior experience with Diltiazem. A3143. When asked whether he had tested Diltiazem in a mixture of sugar and water to see if it would improve solubility, Dr. Weiner replied, "I would never do that, it would be ridiculous." A3138.

In contrast to Dr. Weiner (who never tested whether a sugar solution would improve the solubility of Diltiazem), Paul Maes (a scientist employed by Biovail) directed a study that demonstrated that the solubility of Diltiazem increased 55% when placed in a 16% sugar-water solution, as opposed to a plain water solution. A3155; A14866–67.

The District Court's Decision

After the trial, the district court entered judgment for Andrx on March 6, 2000. The district court adopted almost verbatim large parts of Andrx's proposed findings of fact and conclusions of law, filed before the district court's summary judgment decision. Without any explanation, the district court reversed its own prior decision on claim construction by adopting the following findings and conclusions Andrx proposed:

53. The term "admixture" means two or more items are commingled and interspersed to obtain a homogeneous product.
54. The term "homogeneous" means that samples of the product taken anywhere throughout the product should have the same compositions.
55. The term "wetting agent" is defined as any of a group of surface active agents which, when added to a liquid, cause the liquid to spread more easily over or penetrate into, a solid surface. Weiner testimony; Banakar testimony.

A11.

12. Based on the '791 patent claim language, the specification of the '791 patent and the prosecution history which led to the issuance of the '791 patent, it is clear that the claims of the '791 patent require that the wetting agent and diltiazem be in admixture in the dry state.

A19.

Thus (without any explanation of why it switched to a claim construction inconsistent with its reasoning, opinion, and decision on the motion for summary judgment) the district court held that claim 1 only read on the formulation in the "dry state," effectively re-wrote the claim by replacing the word "admixture" with the phrase "***homogeneous*** admixture ***in the dry state during manufacture and before ingestion,***" and interpreted the term "wetting agent" contrary to the express definition set forth in a Markush group in the claim itself.

SUMMARY OF ARGUMENT

Claim element 1[c] of the '791 patent specifically requires, "an effective amount of a wetting agent in admixture with the one or more Diltiazem salts to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein." This element describes how the compound performs after ingestion. For this reason, the district court construed claim 1 to cover post-ingestion infringement when it denied Andrx's summary judgment motion. Nonetheless, and with no explanation, the district court erroneously construed the claim ***after*** trial to limit it to the pre-ingested form. Also, although claim 1 defines sugar as a "wetting agent" in a Markush group, the district court erroneously held that sugar could be a "wetting agent" only in the "dry" state. In addition, the district court erred by importing the extraneous limitation that the admixture must be "homogeneous."

The district court ignored experimental evidence offered by Biovail, and admissions of Andrx's experts, both of which established that an admixture formed after the Andrx ANDA product was ingested. The district court ignored scanning electron micrographs that showed the sucrose in the core of Andrx's ANDA product dissolving 20 minutes after ingestion. Despite this evidence, the

district court made the clearly erroneous finding that Biovail failed to prove that an admixture of sugar and Diltiazem hydrochloride formed after ingestion.

The district court also erred in applying prosecution history estoppel, where the record fails to demonstrate that Biovail gave up the scope of equivalents at issue here. In this respect, based on a gross oversimplification of the prior art, the district court erred in concluding that Andrx's product was the same as the prior art. Finally, the district court erred in refusing to find infringement under the doctrine of equivalents by ignoring the admitted bioequivalence of Andrx's ANDA product and by ignoring the insubstantiality of differences between Andrx's ANDA product and claim 1 of the '791 patent.

ARGUMENT

On appeal from a bench trial, the district court's conclusions of law, such as its claim construction, are reviewed without deference and its factual findings are reviewed for clear error. *See* FED. R. CIV. PROC. 52(a). An ultimate finding based on an erroneous legal standard, such as a judgment of noninfringement based on an improper claim interpretation, is legal error and due to be reversed without the deference of the clear error standard. *See, e.g., Specialty Composites v. Cabot Corp.*, 845 F.2d 981, 986, 989, 6 USPQ2d 1601, 1604, 1606 (Fed. Cir. 1988) (reversing a finding of infringement where there was no clear error in the factual findings but the claim construction was erroneous).

Andrx's submission of its ANDA to obtain approval to engage in the commercial manufacture, use, or sale of its generic version of Tiazac® before the expiration of the '791 is an act of patent infringement if the '791 patent reads on the product Andrx will sell. 35 U.S.C. § 271(e)(2).

I. THE TRIAL COURT ERRED IN CHANGING ITS CLAIM CONSTRUCTION, WITHOUT EXPLANATION, TO LIMIT THE DRUG TO IT'S PRE-INGESTED FORM WHILE IGNORING DEFINITIONS IN THE CLAIM AND IMPORTING EXTRANEOUS LIMITATIONS FROM THE SPECIFICATION.

When it denied Andrx's motion for summary judgment, the district court construed the claims to cover post-ingestion forms of Andrx's ANDA product. A2746–48. After the trial, however, and with no explanation, the district court

held that the claim could only cover the pre-ingestion form of Andrx's ANDA product. In doing so, the district court erroneously relied on expert testimony to construe the claims, in derogation of the clear language in the claims themselves and in the specification of the patent.

A. NOTHING LIMITS CLAIM 1 TO THE PRE-INGESTED DRUG.

A claim to a drug formulation may cover an accused drug after it has been ingested. *Zenith Labs, Inc. v. Bristol-Myers Squibb Co.*, 19 F.3d 1418, 1421–22, 30 USPQ2d 1285, 1287–88 (Fed. Cir. 1994). Here, Claim 1 must be so construed.

Claim 1 requires that an "effective amount of a wetting agent in admixture with one or more Diltiazem salts . . . maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein." A3186–87. Clearly, this must happen ***in the gastrointestinal tract***. First, the "solubility" of Diltiazem is a characteristic or quality that is meaningful only in the liquid environment of the gastrointestinal tract. Second, given the extended release form of the drug claimed in the '791 patent, it makes no sense to exclude admixtures that occur in the gastrointestinal tract.

Nothing in the prosecution history excludes this construction. Andrx argued below that claim 1 cannot be construed to cover post-ingestion infringement

because applicants argued during prosecution of the grandparent application that issued as U.S. Patent No. 5,288,505 ("the '505 patent") that their manufacturing process differed from that disclosed in the Debregeas '596 patent. First, that argument was not made with respect to the claim at issue. Second, with respect to other composition claims, the examiner specifically ***rejected*** that argument and ***refused*** to allow any claims to issue on that basis. A14496. No reasonable competitor could rely on an unsuccessful argument, rejected by the examiner, and not reflected in the claim as issued as surrendering subject matter otherwise reasonably within the scope of the claims.

In *Zenith*, the Court rejected a similar argument concerning the prosecution history. 19 F.3d at 1425, 30 USPQ2d at 1291. The claim at issue in *Zenith* was for a chemical composition with certain x-ray diffraction properties. *Id.*, 19 F.3d at 1420, 30 USPQ2d at 1286. During prosecution of that patent, the patentee "emphasized the superior manufacturing-related benefits of the pre-ingested form" of the drug. *Id.*, 19 F.3d at 1421, 30 USPQ2d at 1287. The accused infringer argued that the patentee relinquished coverage of any forms of the drug that did exhibit these manufacturing-related characteristics, including any form of the drug formed in a patient's stomach. *Id.* The Court rejected the infringer's argument because "[t]he claim as written and allowed simply describes a compound having specified chemical properties." 19 F.3d at 1421, 30 USPQ2d at 1288. The

Court in *Zenith* held that the claim was for a compound, and that there was nothing in the language of the claim that limited it to the pre-ingested form of the compound. 19 F.3d at 1422, 30 USPQ2d at 1288.

B. ALTHOUGH THE CLAIM ITSELF DEFINES SUGAR AS ONE OF ITS "WETTING AGENTS," THE DISTRICT COURT ERRONEOUSLY HELD THAT SUGAR IS A WETTING AGENT ONLY IN ITS DRY STATE.

The district court erroneously accepted Andrx's argument that sucrose is a "wetting agent" only in its dry state. A12. Claim construction begins with the language of the claim itself. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582, 39 USPQ2d 1573, 1576 (Fed. Cir. 1996) ("First, we look to the words of the claims themselves, both asserted and nonasserted, to define the scope of the patented invention."). Here, ***the claim itself*** identifies sugars as one type of "wetting agent" as that term is used in the '791 patent. Claim element 1[e] is a Markush group which reads in part "wherein the ***wetting agent*** is selected from the group consisting of sugars" and other specified materials. A Markush group defines a set of alternatives, which the patentee here called "wetting agents." *See*, LANDIS, MECHANICS OF PATENT CLAIMS DRAFTING § 50 (Robert C. Faber, ed., 1997) ("Markush claims ***define*** alternative chemical ingredients that can be used in a compound, composition, alternative steps in a process, or alternative choices for an article.") (emphasis added). Of course, patentees are free to define terms provided the definition is set forth clearly. *Vitronics*, 90 F.3d at 1582, 39 USPQ2d

at 1576 ("Although words in a claim are generally given their ordinary and customary meaning, a patentee may choose to be his own lexicographer and use terms in a manner other than their ordinary meaning, as long as the special definition of the term is clearly stated in the patent specification or file history.").

The patent specification confirms that "saccharose," the very compound in Andrx's product, is "[a]mong the wetting agents associated with the Diltiazem or salt thereof in the beads." A3184. Similarly, the file wrapper confirms that the these claims were allowed with the understanding that the claims defined what are wetting agents in this invention. Thus, the examiner wrote:

> The composition requires a particular type of wetting agent to be effective. Since it is evident that the release profile of the drug is determined by the particular wetting agents in admixture, the limitations of claim 28 are considered critical and should be incorporated into claim 27 for proper enablement

A3385. Thus, even if the term "wetting agent" has an ordinary meaning to those of skill in the art, the intrinsic evidence of the claims, written description, and prosecution history clearly provide a different, special definition.

The trial court erred by permitting Andrx to ***contradict*** this intrinsic definition with the testimony of Dr. Wiener, Andrx's supposed expert in surface chemistry. He testified and the trial court found that sugar is not a wetting agent when it is wet, i.e., the ***only*** time it would be available "to maintain the solubility of Diltiazem in each bead" as required by claim element [d]. A3186–87. Permitting

expert testimony to alter the scope of the claims required by the intrinsic evidence is legal error. *Hormone Research Found. v. Genentech, Inc.*, 904 F.2d 1558, 1563, 15 USPQ2d 1039, 1043 (Fed. Cir. 1990) ("It is a well-established axiom in patent law that a patentee is free to be his or her own lexicographer and thus may use terms in a manner contrary to or inconsistent with one or more of their ordinary meanings.") (citations omitted). The court in *Vitronics* stated this principle forcefully:

> However, as we have recently re-emphasized, extrinsic evidence in general, and expert testimony in particular, may be used only to help the court come to the proper understanding of the claims; it may not be used to vary or contradict the claim language. Nor may it contradict the import of other parts of the specification. Indeed, where the patent documents are unambiguous, expert testimony regarding the meaning of a claim is entitled to no weight.

Vitronics, 90 F.3d at 1584, 39 USPQ2d at 1578 (citations omitted). Thus, "regardless of how those skilled in the art would interpret a term in other situations, where those of ordinary skill, on a reading of the patent documents, would conclude that the documents preclude the term being given the meaning propounded by the expert witnesses, we must give it the meaning indicated by the patentee in the patent claim, specification and file history." *Vitronics*, 90 F.3d at 1585, 30 USPQ2d at 1579. The district court here, just like the district court in *Vitronics*, erroneously received expert testimony to alter the unambiguous language of the claims, written description, and prosecution history.

C. THE DISTRICT COURT ERRED BY IMPORTING THE EXTRANEOUS LIMITATION "HOMOGENEOUS" INTO THE CLAIM WHEN INTERPRETING THE UNAMBIGUOUS WORD "ADMIXTURE"

The district court also erred in adopting Andrx's proposed claim construction that Andrx defines "admixture" to mean that two or more items are commingled and interdispersed to obtain a homogeneous product, and in turn defines "homogeneous" to mean that samples of the product taken anywhere throughout the product must have the same composition.

"Claim terms are to be interpreted so as to give the terms their ordinary meaning, absent some clear special definition." *Enercon GmbH v. ITC*, 151 F.3d 1376, 1384–85, 47 USPQ2d 1725 , 1731–32 (Fed. Cir. 1998) (term "rotating" not limited to a special type of phase shift disclosed in the written description of the patent, but given its ordinary meaning). While failing to credit the clear and unambiguous definition of the term "wetting agent" in the claim (see argument *supra*), the court also erroneously imported the limitation "homogenous" into the claim.

There is no "clear special definition" in the '791 patent that requires the admixture to be homogeneous. Indeed, the word "homogeneous" is not used either in the claims or the written description in the specification of the '791 patent. Rather, in claim 1, the "admixture" is given context in claim element [d] by func-

tional language that explains the result of the admixture in the gastrointestinal tract:

> an effective amount of a wetting agent ***in admixture*** with the one or more Diltiazem salts ***to maintain the solubility*** of the Diltiazem in each bead, ***ensuring*** that the ***solubility*** of the Diltiazem is ***unaffected by the pH*** of the ***gastrointestinal tract or other adverse conditions*** which the composition will meet therein.

A3187 (emphasis supplied). From this functional language, it is clear that the admixture must maintain the solubility of Diltiazem in each bead so that it is unaffected by pH or other adverse conditions in the gastrointestinal tract. There is no requirement in the claim, however, that the admixture be homogeneous.

Claim 1 does not require that the admixture be homogeneous. "Admixture" is a common English word, defined as "a product of mixing." *Webster's New Collegiate Dictionary*, page 18 (G&C Merriam Co., 1991). In the context of claim 1, "admixture" is unambiguous, and does not require a special definition. Indeed, in two separate cases, "admixture" has been defined as "a mixture." *Leesona Corp. v. Varta Batteries, Inc.*, 522 F. Supp. 1304, 1325–25 (S.D.N.Y. 1981); *Moores Business Forms, Inc. v. Wallace Computer Services, Inc.*, 14 USPQ2d 1849, 1851, 1856–57 (N.D. Ind. 1989) (no indication in specification or prosecution history that "admixture" have extraordinary meaning; "admixture" construed to mean mixture; "while the prosecution history describes the mixing process, it does not define the term 'admixture'"). Andrx's experts did not point to a single

scientific dictionary that defines an admixture as necessarily being homogeneous. The '619 patent shows at column 3, line 10, that those skilled in the art use the word "homogeneous" when they intend that components that are blended be homogeneous. A14931.

In contrast, the definitions of homogeneous proffered by Andrx's experts (without any literature support) relate to processes mixing dry substances together to ***formulate*** a solid dosage form. Andrx offered no evidence to show that those "manufacturing-related" definitions have any applicability to dynamic phenomena that takes place in solution in the gastrointestinal tract. In the context of claim 1, "admixture" is unambiguous, and does not require a special definition.

The Court in *Vitronics* indicated that expert testimony on the meaning of terms is inherently suspect. "As compared to expert testimony, which often only indicates what a particular expert believes a term means, prior art references may also be more indicative of what all those skilled in the art generally believe a certain term means." *Vitronics*, 90 F.3d at 1584, 39 USPQ2d at 1579. Neither Dr. Weiner nor Dr. Banakar offered any prior art references to support their interpretation that the word "admixture" means homogeneous. Further, their purported reliance 21 C.F.R. § 211.110 is entirely misplaced. That regulation relates only to "Sampling and testing of ***in process*** materials and drug products." *Id.* (emphasis added). Moreover, that section does not define the word "admixture" to be "ho-

mogeneous." It simply requires that to assure batch uniformity and integrity of drug products, that there must be control procedures to validate performance of manufacturing processes, and that those control procedures include "adequacy of mixing to assure uniformity and homogeneity." *Id.* Indeed, this phrase shows that not all mixing is homogeneous. Regardless, this definition is entirely irrelevant to Claim 1, because Andrx's experts agree that Claim 1 is not a manufacturing or process claim. A3119; A3143.

The court's claim interpretation also errs because it limits claim 1 to the preferred embodiment disclosed in the patent, particularly to the extent it relied on the PTO declaration of Deboeck. The declaration of Deboeck describes experiments made with the preferred embodiment disclosed in examples 2 and 4 of the '791 patent. Patent claims, however, are not limited to preferred embodiments. *Enercon*, 151 F.3d at 1384–85, 47 USPQ2d at 1731–32.

The court erroneously concluded that the prosecution history requires that claim 1 calls for a "homogeneous" admixture because it misinterpreted the effect of certain statements in the prosecution history. As explained to the PTO, the '596 patent teaches a system in which the water would not contact the sugar in the core until the Diltiazem was gone or there was no further need for a wetting agent. This is primarily because the '596 patent teaches the use of shellac in the membrane of the formulation disclosed. Shellac is a material that inhibits the

penetration of water. Moreover, the '596 patent is directed to a Diltiazem hydrochloride formulation with alternating layers of dry Diltiazem hydrochloride and a PVP solution. Therefore, Biovail disclaimed the '596 patent formulation in that the sugar core does not come into contact with water and become associated with Diltiazem hydrochloride to act as a wetting agent. As noted to the PTO, water hydrates the sugar core of the '596 patent formulation only after all of the Diltiazem hydrochloride is released from the layers of that formulation. As such, the '596 patent formulation does not teach an admixture of wetting agent and Diltiazem hydrochloride.

Nothing in the prosecution history of the '791 patent requires that "admixture" in claim 1 be defined to be homogeneous. The '791 patent was the second patent to issue from an original patent application filed on June 26, 1991. The first patent that issued from that application was U.S. Patent No. 5,288,505. The continuation application that resulted in the issuance of the '791 patent was filed during the prosecution of the application for the '505 patent. The original application, filed on June 26, 1991, which ultimately became the '505 patent, included 11 claims. A14440–42. On March 23, 1992, the examiner issued an office action rejecting claims 1–11 as being anticipated by Debregeas et al, U.S. 4,960,596. A14466-70. After those claims were rejected, the applicants submitted an amendment, which cancelled claims 1–11 of the original application, and

added claims 12–30. A14473–91. None of the claims in the original application or this amendment recited that the wetting agent was in admixture with Diltiazem. Instead, the inventors distinguished Debregeas by the manner in which it was made, and on the grounds that it did not disclose a wetting agent and that it had a different membrane.

The examiner's record of the April 7, 1993 interview during the prosecution of the '505 patent does not suggest that "admixture" must be defined as "homogeneous." To the contrary, at the time of that interview, the claims did not include the word "admixture." A14505; 14473–78. The claims described the beads as "comprising a) an effective amount of said one or more Diltiazem salts as an active ingredient, and b) a wetting agent . . . ." Thus, the examiner's summary cannot define "admixture," because that term was not in the claims at the time of the interview.

After the April 7, 1993 interview in the application for the '505 patent, the claims were amended to include the term "admixture." A14507–27. In that regard, the claim discussed in the "Remarks" section of the amendment filed after the interview included the language "the beads consisting essentially of ***in admixture together***: (a) an effective amount of Diltiazem or said one or more salts thereof as an active ingredient, and (b) an effective amount of a wetting agent, wherein said wetting agent is selected from the group . . . ." (emphasis added).

A14508–512. Nowhere in the remarks section was the word "admixture" defined as "homogeneous." Indeed, the words "mixture" and "admixture" were used to describe several different things on page 9 of the "Remarks" section of the amendment, A14517, none of which need be homogeneous.

Applicants pointed out that the sugar seed of the Debregeas '596 patent was "***a mixture of saccharose or fructose and starch***." On the same page, applicants also pointed out that "in Debregeas et al, Diltiazem is ***in admixture*** with only PVP, and not with the 'core' [the sugar/starch seed] of that composition." There is no evidence that "admixture" in either sense was intended to be limited to a "homogeneous" admixture. Finally, on the same page, Applicants then pointed out that, in contrast, the formulation of the invention "contains Diltiazem or one or more salts thereof ***in admixture together*** with the wetting agent." A14515. There is no evidence that applicants intended that the word "mixture" or "admixture" be limited to "homogeneous" in that context. The word "admixture" is clearly used in its ordinary sense, which is not limited to a "homogeneous" admixture.

Further, applicants argued that the saccharose in the central core of the Debregeas bead "***cannot*** act as a wetting agent because in order to do so the saccharose must be ***mixed*** with the Diltiazem and therefore saccharose must be ***in solution with Diltiazem.*** Unfortunately in this system saccharose can only end up ***in***

solution after all the layers of Diltiazem are dissolved." A14521 (emphasis added). The applicants ***never*** argued that the ***claim*** distinguished Debregeas because ***the claim*** required that the wetting agent must be homogeneously admixed with the wetting agent. On the contrary, applicants argued only that the wetting agent must be "***mixed with***" or "***in solution with***" the Diltiazem.

Following the receipt of the Deboeck declaration, the examiner could have required applicants to insert the word "homogeneous" into the claims if he had believed that the invention was confined to homogeneous admixtures. No such requirement was made. Instead, the examiner specifically said that he was ***not*** relying on the contents of that declaration as a basis for allowance of any claims. A14528.

During his deposition, Mr. Deboeck explained that the remarks about the homogeneous mixing related to the process of ***manufacturing*** the ***preferred embodiment:***

> Q. Why is it essential that the components of the core be homogeneously mixed?
>
> A. Because — this example. This is data from Example No. 2, and because it is the preferred embodiment done by extrusion spheronization. If in that particular step the mixing is not homogeneous as good as possible we cannot produce final dosage forms within the specification of content.

A17007.

For the reasons set forth above, the court's claim construction that "admixture" must be defined to be "homogeneous" is erroneous.

II. ANDRX LITERALLY INFRINGES THE '791 PATENT BECAUSE ANDRX'S SUGAR CORE DISSOLVES TO FORM AN ADMIXTURE WITH DILTIAZEM HYDROCHLORIDE THEN MAINTAINS THE SOLUBILITY OF THE DILTIAZEM IN THE GASTROINTESTINAL TRACT.

Biovail proved at trial that every element of the claims of the '791 patent are found in the accused Andrx product. Contrary to Andrx's arguments, Andrx's product is not the same as the prior art. Andrx's product does not mix a Diltiazem salt with an organic acid, as is shown in the '619 or '240 patents (DTX 7,8). Andrx's beads do not have alternating layers like the prior art beads in the '619, '240, or '596 patents.

A. IT IS UNDISPUTED THAT ANDRX'S ALLEGEDLY BIOEQUIVALENT PRODUCT SATISFIES CLAIM ELEMENTS [A], [B], [D], AND [E].

Andrx's ANDA shows, and Dr. Langer testified, and Andrx's expert, Dr. Weiner admitted, that Andrx's ANDA product is a 24-hour extended release pharmaceutical formulation comprising beads containing Diltiazem hydrochloride. A12787; A3066; A3145.

Andrx's ANDA shows, and Dr. Langer testified, and Dr. Weiner admitted, that Andrx's ANDA product has beads containing Diltiazem hydrochloride, which is a pharmaceutically-acceptable salt of Diltiazem. *Id.*

Andrx's ANDA shows, and Dr. Langer testified, and Dr. Weiner admitted, that beads of Andrx's proposed generic equivalent to Tiazac® are coated with a microporous membrane comprising hydroxypropylmethylcellulose, a water-soluble or water-dispersible polymer or copolymer, Eudragit NE-30-D, a water-, acid-, and base-insoluble polymer, and talc and magnesium stearate, both pharmaceutically-acceptable adjuvants. A12684; A3066–67; A3145. This membrane is exactly the same as the membrane disclosed in Example 4 of the '791 patent at Column 6, line 55 – Column 7, line 8. A3066–67. When Andrx began developing an equivalent to Tiazac®, it tried unsuccessfully to avoid using the same coating used in Tiazac®. A15637–38. Because those attempts failed, Andrx switched to using Eudragit NE-30-D as its coating, which is the same principal polymer component as in Tiazac®. A15637–38.

B. THE DISTRICT COURT CLEARLY ERRED IN FINDING THAT THE SUGAR IN ANDRX'S PRODUCT DOES NOT SATISFY THE REQUIREMENT OF A "WETTING AGENT," WHICH CLAIM 1 DEFINES TO INCLUDE SUGARS.

The trial court's findings 61–69 and 76–79, (A12–13), about the efficacy of sugar as a wetting agent, are based on its erroneous claim construction which failed to recognize, as explained above, that sugar is defined as a wetting agent in the claims.

As the term "wetting agent" is used in the claims, the point is not to ***dissolve*** Diltiazem, but to ***maintain*** its solubility until it is released into the gastro-

intestinal system. All of the trial court's findings reflect the untested opinions of Andrx's experts about how they would expect sugar to act when Diltiazem is dissolving. That testimony, however, does not reflect what happens in the accused Andrx product.

In the Andrx product, the Diltiazem is originally in the form of Diltiazem hydrochloride. It is undisputed that Diltiazem hydrochloride is very soluble. The problem is not getting the Diltiazem hydrochloride to dissolve. The problem is that as the plain Diltiazem is no longer soluble as it dissociates from Diltiazem hydrochloride in less acidic parts of the gastrointestinal tract.

Once the Diltiazem hydrochloride and the sugar are dissolved together, the sugar tends to maintain the solubility of the Diltiazem (as opposed to the Diltiazem hydrochloride). Although the trial court found (Nos. 77, 79) sucrose does not function as a wetting agent in solution, A14, it apparently based that finding on the opinion of Andrx's experts. Those experts, however, only offered opinions as to whether sugar would help to dissolve Diltiazem initially, not as to whether it would help it remain in solution. Moreover, the unexpectedness of result of maintaining the solubility of plain Diltiazem is not a basis for finding non-infringement, but instead an objective indicia of the patentability of the subject matter.

Biovail introduced uncontroverted experimental evidence of a test conducted at Biovail under Mr. Maes' direction. Mr. Maes acknowledged that this unexpected result runs contrary to the expected behavior for Diltiazem, but that is why scientists run experiments. A3161. That test proved that Diltiazem became 55% more soluble in a solution of 16% sucrose. The district court entirely ignored the hard experimental data provided by the results of this test, and did not explain in its findings why it accepted Dr. Weiner's untested postulations when contradicted by Mr. Maes test, which was the only experiment performed on the subject. In post trial briefing, Andrx took exception that the experiment was conducted with the Diltiazem base, rather than Diltiazem hydrochloride.

Andrx's purported exception proves the rule. As, Dr. Langer testified, "as you get to the more higher pH's, you have less Diltiazem hydrochloride and more Diltiazem, so it becomes less soluble as you start going through the GI tract." A3067. And Paul Maes testified that "in the GI tract, a significant portion of Diltiazem hydrochloride is transformed into Diltiazem." A3160. In addition, claim element 1[c] requires that the admixture "maintain the solubility of *Diltiazem* in each bead," not the Diltiazem salt. Further, Mr. Maes testified that the experiment was performed in the ordinary course of business at Biovail, in accordance with Biovail's standard operating procedures, and that if the experimental error were unacceptable, the report would not have been signed. A3160–62. Thus, Mr.

Maes' experiment demonstrates that a sucrose solution helps maintain the solubility of Diltiazem in the lower part of the gastrointestinal tract, which is what claim element 1[c] requires. A3155; A14866–67.

For the reasons explained above, the sugar satisfies the element of being a wetting agent when mixed with Diltiazem or Diltiazem hydrochloride, regardless of whether the sugar is wet or dry when this mixing first occurs, because it is defined as a wetting agent in the claim and because uncontested evidence shows that once mixed the sugar will tend to maintain the solubility of Diltiazem.

C. THE TRIAL COURT CLEARLY ERRED IN FINDING THAT DILTIAZEM HYDROCHLORIDE DOES NOT ADMIX WITH SUGAR IN THE BODY.

Andrx's product is, for all intents and purposes, a copy of Biovail's Tiazac® product, with one small change that does not avoid infringement.

Nothing in Andrx's product other than its sugar core could function to maintain the solubility of Diltiazem. It does not use a layered structure as shown in the prior art, and does not include an adjuvant of organic acid. Accordingly, the fact that Andrx asserts bioequivalency shows the efficacy of its sucrose as a wetting agent "to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein."

The trial court's findings 70–75 about whether sugar mixes with the Diltiazem forms in the body A13–14, are clearly erroneous.

Based on a series of related experiments run by Dr. Mathiowitz, A3069–70; A13453; A13463–64; A13609–47, Dr. Langer testified that after the Andrx ANDA product has been ingested, water penetrates the membrane of the microcapsules, penetrates to the sugar starch core, dissolves the sugar, and the sugar forms an admixture, within the membrane, with a Diltiazem salt (Diltiazem hydrochloride). A3069–70. Dr. Weiner conceded that it is almost certainly true that when liquid reaches the sugar core in the gastrointestinal tract, the sucrose then mixes in with the Diltiazem hydrochloride in the bead of the Andrx ANDA product while they are still in the membrane, although he argued that the mixture is not homogeneous. A3145.

The district court's finding No. 74 that these tests are not reliable, A14, is clearly erroneous. In the first test, beads became soft after they were immersed in a solution — a simple, initial matter of observation. Product weight loss studies done by Dr. Mathiowitz show that something other than Diltiazem leaves the Andrx beads at various time intervals (1, 2, 3, 4, 6, 8, 10, 12, 16, and 20 hours). A3069–70; A13453; A13464. Dr. Weiner's criticisms of the experimental error in this test are refuted by the experimental error in his own article. A3146; A14857–64. Moreover, Dr. Weiner's criticisms are undercut by his admission

that he, too, believes that the sugar and Diltiazem salt mix in the membrane after the Andrx ANDA product is ingested. A3145. In addition, the test was designed to demonstrate that something other than Diltiazem comes out of the Andrx beads at various times.

The district court's finding No. 75 that Biovail's Scanning Electron Micrographs ("SEM's") do not show that a homogeneous admixture is formed in the Andrx product, A14, is clearly erroneous. First, under the proper claim construction it is irrelevant that the mixture is homogeneous. Second, the SEM's show that sucrose leaves the sugar/starch seed with the membrane still intact. A3069–70. Finally, the glucose tests confirm that sucrose comes out of the beads. A13463. Dr. Mathiowitz testified that in this test, she used a very small amount of sodium azide to inhibit bacterial growth. A3061. Andrx presented ***no*** tests and ***no*** experimental data to show that the amount of sodium azide Dr. Mathiowitz added to the solution would have ***any*** effect on her detection of glucose.

The trial court's findings 77 and 78 about the efficacy of sugar to maintain the solubility of Diltiazem in the Andrx product are clearly erroneous. Andrx's own product tests, submitted to the FDA, demonstrate that its product is a "bio-equivalent" of Biovail's Tiazac® product. Dr. Langer also testified that the bio-availability studies from Andrx's ANDA demonstrate that the admixture of sugar

and Diltiazem hydrochloride in the Andrx bead maintains the solubility of Diltiazem in each bead so that it is unaffected by the pH of the gastrointestinal tract or other adverse conditions. A3070–71; A3516; A6287.

Even if claim 1 did require that the "admixture" be homogeneous (which it does not), the admixture that forms in the Andrx product after it is ingested is homogeneous, as Dr. Weiner has defined that term. Dr. Weiner defined homogeneous to mean anything that has been mixed for about 15 minutes. A3133. Dr. Weiner agreed that United States Pharmacopeia (the "USP") defines homogeneous to be between 85% and 115%. A3150. Dr. Mathiowitz testified in rebuttal that, given Dr. Weiner's definition of homogeneous, that the admixture in the Andrx membrane is homogeneous after it has been in the gastrointestinal tract for at least 5 hours. A3164. After 5 hours, SEM's show everything is completely mixed. A3165. Further, in her cross examination, Dr. Mathiowitz testified that she did not know how Andrx defined homogeneous, but her FTIR tests showed that Diltiazem was homogeneously distributed throughout the bead. A3061. Further, in the declaration of Arthur Deboeck, (which the Trial Court relied on for its determination that the mixture must be homogeneous,) he concluded that his dry mixture of Diltiazem and sucrose was homogeneous, based solely on his measurements of Diltiazem. A14224–34. Dr. Langer testified that he did not know whether the Andrx bead in the picture was homogeneously mixed. A3077.

Dr. Langer's testimony is not contrary, because all he said was that he did not test to determine if sucrose and Diltiazem were homogeneously mixed. A3088. Dr. Langer did not base that earlier testimony on Dr. Weiner's definition of homogeneous at the time he testified. A3165.

Although Dr. Banakar testified that there is "no way that the drug and sucrose will be . . . homogeneously dispersed" after the Andrx drug is ingested, he offered no explanation for his conclusion. The only reason Dr. Weiner gave for his conclusion was that he believes sugar in solution is not a wetting agent for Diltiazem. A3135.

Mr. Deboeck confirmed that making a homogeneous bead was merely "the preferred way to do it," i.e., the preferred embodiment. A16999. Claims are not limited to the preferred embodiments of the invention. *E.g.*, *Enercon GmbH v. ITC*, 151 F.3d 1376, 1384–85, 47 USPQ2d 1725, 1731–32 (Fed. Cir. 1998).

III. THE ANDRX PRODUCT IS EQUIVALENT TO THE PRODUCT CLAIMED IN THE '791 PATENT

"Infringement under the doctrine of equivalents is a factual determination which we review under the clearly erroneous standard." *Ryco, Inc. v. Ag-Bag Corp.*, 857 F.2d 1418, 1426, 8 USPQ2d 1323, 1329 (Fed. Cir. 1988).

The written findings and conclusions of the trial court adopted almost verbatim from Andrx's pretrial submission reflect a lack of careful, independent con-

sideration on the doctrine of equivalents. Those findings and conclusions rely first on a doctrine creatively named "Prior Art Estoppel," which is at best a novel form of defense. The most analogous rule recognized in conventional patent law is that a claim's legitimate scope of equivalents cannot encompass the prior art, but the trial court's decision on the facts of this case misapplied with that body of law by relying on mere superficial similarities. The trial court's application of prosecution history estoppel is also unsustainable. In light of the manifestly deficient legal and factual analysis the trial court mechanically adopted verbatim from findings and conclusions Andrx proposed before trial, the ultimate finding of no infringement under the doctrine of equivalents is clearly erroneous and must be reversed.

A. THE PERMISSIBLE SCOPE OF EQUIVALENTS FOR THE '791 PATENT ENCOMPASSES ANDRX'S PRODUCT, WHICH MAINTAINS THE SOLUBILITY OF DILTIAZEM BY MIXING IT WITH SUGAR.

The trial court analyzed the scope of equivalents permitted by the prior art in terms of a so-called "estoppel" against the patentee, supposedly because "the Andrx formulation was admitted by Plaintiff to be within the scope of the prior art." A23. The sheer improbability of any such admission should have been enough to give the trial court pause before adopting these proposed conclusions. A careful (or even a superficial) review of the facts and law shows that there was no such admission, that there is no such doctrine as "prior art estoppel," that

Andrx's product is not within the scope of the prior art, and that the trial court clearly erred in applying this "prior art estoppel" theory to find no infringement under the doctrine of equivalents.

1. Biovail Never, Ever, Admitted the Andrx Formulation "To Be within the Scope of the Prior Art."

There are, of course, similarities between Andrx's formulation and the prior art, just as there are similarities between Triazac® as claimed in the '791 patent and the prior art. All are medicines. All include Diltiazem hydrochloride. All are round. None are bigger than a breadbox.

Such trivial, superficial similarities do not show that they are all the same thing, or even that they are essentially the same things. The important inquiry must be the extent to which they ***differ***, not the extent to which they may be similar.

The trial court relied on just such trivial, superficial similarity when it found that the patentee admitted that the Andrx formulation was in the prior art. The prosecution history includes that same kind of generalized description of the Debregeas '596 patent, which the trial court quoted in Finding 90. A16. The fact that the same general terms describe the Andrx product does not prove that the product is within the prior art. Such reasoning is simply a logical fallacy.

The fact that two different things may fall within the same generic group does not mean that the two things are the ***same***. The fact that Andrx's product and the Debregeas formulation both have a sugar core, a layer including the active ingredient, and an outer coating likewise does ***not*** mean that the Andrx product is within the prior art, and ***certainly*** cannot support a finding that the patentee admitted that Andrx's formulation was in the prior art.

Several ***different*** patents including those patents listed in findings 88 and 92 disclose a drug manufactured by starting with a sugar seed, then applying materials including the active ingredient such as Diltiazem hydrochloride, then applying an outer coating. A15–16. Presumptively, however, each of those formulations is patentably distinct, inasmuch as each formulation is embodied in a separate patent and each patent is presumed to be valid. Applying the trial court's specious reasoning, the gross similarity between them would be taken as an admission that all but the first were in the prior art.

The trial court's finding, that the patentee admitted Andrx's product to be in the prior art, is a logical fallacy. This is not a decision to credit one witness over another, or a choice between equally viable alternative theories. The trial court's fallacy is clearly erroneous, and cannot serve as the basis for a judgment of noninfringement.

2. *There Is No Such Thing As "Prior Art Estoppel."*

The trial court then compounded its clearly erroneous fact findings with legally incorrect conclusions, including the following:

> 36. The doctrine of prior art estoppel provides a legal limitation on the application of the doctrine of equivalents by mandating that the asserted range of equivalents may not encompass the prior art at the very point at which the claims distinguish from that art.
>
> 37. The doctrine of prior art estoppel prevents the doctrine of equivalents from expanding the scope of the claims to protect subject matter in, or obvious in light of, the prior art. *Athletic Alternatives, Inc. v. Prince Mfg. Inc.*, 73 F.3d 1573, 1582 (Fed. Cir. 1996).
>
> 38. Thus, because the Andrx formulation was admitted by Plaintiff to be within the scope of the prior art, the doctrine of equivalents cannot be asserted by Plaintiffs to bring the Andrx formulation within the scope of the '791 patent claims. *Stewart-Warner*, 767 F.2d at 1572; *Athletic Alternatives*, 73 F.3d at 1582.

A22–23. Patent jurisprudence knows no doctrine by the name "prior art estoppel." A search on Lexis or Westlaw shows that the phrase has never appeared in ***any*** reported decision of ***any*** federal court as used here. Yet, this non-doctrine is the basis for findings 88–93 (A15–16) and conclusions 36–41 (A23–24), which are central to the district court's doctrine of equivalents analysis. Although the district court's error is more fundamental than merely using the wrong name for a doctrine, its verbatim adoption of such unsupported and unsupportable proposed conclusions from Andrx does suggest a lack of independent evaluation by the trial

court, particularly on proposed findings and conclusions offered before any evidence was even received at the bench trial. *See Anderson v. City of Bessemer City*, 470 U.S. 564, 572 (1985) ("We . . . have criticized courts for their verbatim adoption of findings of fact prepared by prevailing parties, particularly when those findings have taken the form of conclusory statements unsupported by citation to the record."); *United States v. El Paso Natural Gas Co.*, 376 U.S. 651, 656–57 (1964) (admonishing that proposed findings "were 'mechanically adopted,' . . . and do not reveal the discerning line for decision of the basic issue in the case."); *accord, United States v. Marine Bancorporation*, 418 U.S. 602, 615, n. 13 (1974) ("In adopting, verbatim, proposed findings of fact in a complicated . . . action, the District Court failed to heed this Court's admonition voiced a decade ago.").

a) The Authority Cited By Andrx and Mechanically Adopted Verbatim By the District Court Does Not Support Conclusions 36–41.

The district court based its conclusion 36–41 on *Athletic Alternatives, Inc. v. Prince Mg., Inc.*, 73 F.3d 1573, 1582, 37 USPQ2d 1365, 1373 (Fed. Cir. 1996) and *Stewart-Warner Corp. v. City of Pontiac*, 767 F.2d 1563, 226 USPQ 676 (Fed. Cir. 1985). Neither case supports those conclusions.

While the statement in conclusion 37 appears in background discussion in *Athletic Alternatives*, the ***holding*** in that case actually applies the rule that (as a

corollary to the "all limitations" rule) the doctrine of equivalents cannot encompass subject matter ***specifically excluded*** from the scope of the claims. *Id.*, 73 F.3d at 1582, 37 USPQ2d at 1373 ("As a corollary to the 'all limitations' rule discussed above, we have held that "the concept of equivalency cannot embrace a structure that is specifically excluded from the scope of the claims."). The rule in *Athletic Alternatives* has no application on the facts of ***this*** case.

Likewise, nothing in *Athletic Alternatives* is like the district court's conclusion 38. As explained above, the holding in *Athletic Alternatives* was not based on an admission or a conclusion that the accused product was within the scope of the prior art. *Stewart-Warner* also applied an analysis like that in *Athletic Alternatives* to conclude that there could be no equivalents there because "a structure that does not operate in real time cannot be found equivalent to one that does in this case," *Stewart-Warner*, 767 F.2d at 1572, 226 USPQ at 682, although it also considered prosecution history estoppel and the range of equivalents permitted by the prior art.

The proper analysis here must focus on cases considering whether an asserted scope of equivalents was within the prior art. As explained below, such cases show that the Andrx product clearly is within the legitimate scope of equivalents for the '791 patent in this case.

b) The Prior Art Does **Not** *Exclude Andrx's Product From the Scope of Equivalents Because Andrx's Product Maintains the Solubility of Diltiazem in a Way Different from Prior Art and the Same as the '791 Patent.*

Of course, the prior art in some circumstances may restrict the permissible scope of equivalents. *Ryco*, 857 F.2d at 1426, 8 USPQ2d at 1330 (Fed. Cir. 1988) ("[T]he doctrine [of equivalents] will not be used to extend a patent claim to cover a device in the public domain, i.e., found in the prior art applicable to the patent."). This restriction, however, is not in the nature of an estoppel based on "admissions" of the patentee, but instead embodies the principle that "a patentee should not be able to obtain, under the doctrine of equivalents, coverage which he could not lawfully have obtained from the PTO by literal claims." *Wilson Sporting Goods Co. v. David Geoffrey & Assocs.*, 904 F.2d 677, 684, 14 USPQ2d 1942, 1948 (Fed. Cir. 1990).

"This issue — whether an asserted range of equivalents would cover what is already in the public domain — is one of law, which we review de novo . . . ." *Wilson*, 904 F.2d at 683, 14 USPQ2d at 1948. The *Wilson* case suggested a particular analytical technique using a hypothetical claim. That approach may be considered more precise than comparing the accused product to the prior art, as was done in *Ryco*. *See Wilson*, 904 F.2d at 684, 14 USPQ2d at 1948. However, "[n]othing in *Wilson* mandates its use as the only means for determining the ex-

tent to which the prior art restricts the scope of equivalency that the party alleging infringement under the doctrine of equivalents can assert." *Conroy v. Reebok Intl., Ltd.*, 14 F.3d 1570, 1576, 29 USPQ2d 1373, 1378 (Fed. Cir. 1994). Here, comparing the Andrx product to the prior art is sufficient to show that it is within the legitimate scope of equivalents to the '791 patent.

Just because the accused product superficially resembles the prior art does not preclude infringement under the doctrine of equivalents. *Ryco*, 857 F.2d at 1426, 8 USPQ2d at 1329–30. In *Ryco*, the accused product and prior art both featured a helical arrangement of teeth in rotors. *Id.* To determine the permissible scope of equivalents, however, the Court in *Ryco* looked closer to assess the ***function*** performed. *Id.* ("Looking closer, however, it is apparent that the two are similar in name only and not in function."). Because the accused product in *Ryco* actually ***functioned*** differently from the prior art, the Court ruled that product was not beyond the permissible scope of equivalents. "To say that Ryco is practicing the prior art and therefore does not infringe is to put form over function." *Id.*

In this case, the functional limitation in element 1[c] of the patent supplies the function to use to compare the Andrx product to the prior art. Biovail has charged Andrx with infringement on the basis that it has "an effective amount of a wetting agent in admixture with the one or more Diltiazem salts to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltia-

zem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein." A prior art reference that does not have this (an effective amount of a wetting agent performing those functions of maintaining the solubility of Diltiazem and ensuring it is unaffected by the gastrointestinal pH and other adverse conditions) does not restrict the scope of equivalents for the '791 patent. If the prior art reference does not perform those functions in that way, the '791 patent is distinguished over them and there is no risk that the patentee has "obtain[ed], under the doctrine of equivalents, coverage which he could not lawfully have obtained from the PTO by literal claims." *Wilson*, 904 F.2d at 684, 14 USPQ2d at 1948.

3. ***Andrx's Product Does Not Maintain the Solubility of Diltiazem Using Any Technique Taught in the Prior Art.***

Andrx's product is not the same as the prior art. Andrx's product does not mix a Diltiazem salt with an organic acid, as is shown in the prior art. Andrx's beads are not "layered," like the prior art beads. Andrx does not use an enteric coating, like the prior art.

a) Andrx Does Not Use an Organic Acid Adjuvant, a Combination of Microcapsules, or Alternating Layers Like Cardizem Products.

One technique disclosed in the prior art for maintaining the solubility of Diltiazem is the use of alternating layers of active ingredient and coating material

to keep Diltiazem in the form of Diltiazem hydrochloride. One example of such an "alternating layers" solution is disclosed in U.S. Patent No. 4,721,619 ("the '619 patent"), which covers "sustained release," twelve-hour Diltiazem marketed under the trade name Cardizem SR®. The '619 patent describes (as Example 1 and Example 2) two similar ways to make Cardizem SR®. Cardizem SR® includes a homogenous powder of Diltiazem hydrochloride, an organic acid (such as fumaric acid), and a lubricant (such as talc). The drug is made by building layers of this homogenous powder, with each layer separated from and attached to the next layer with a coat of polymeric material. The first layer of coating is attached to a sugar/starch seed, then 50 to 200 additional alternating layers of powder and coating are attached to it. A14918. The entire bead is then encased in a membrane of 20 to 40 layers of a similar coating composition.

Cardizem SR® as described in the '619 patent has several characteristic features. It uses an organic acid in the active ingredient layers to maintain the solubility of its Diltiazem in the gastrointestinal tract, whereas both the Andrx product and the '791 patent use one of several wetting agents listed in the '791 patent. A3086. It is built in layers, with each layer encased in its own membrane of coating solution. The solvent of the polymer solution used to make the membrane includes organic solvents, such as isopropanol, methanol, acetone, and methylene chloride, which are dangerous because they are flammable and toxic.

All traces of the solvent must be eliminated from the final product, which is administered orally. Those solvents are also environmentally hazardous.

Thus, neither Cardizem SR® nor Cardizem CD® nor the '619 patent excludes the Andrx product from the scope of equivalents for the '791 patent.

b) Andrx Does Not Use an Enteric Coating Like Debregeas.

Andrx also claimed that its product is like the prior art Debregeas '596 patent. Debregeas, however, relies on a special coating that works differently from the '791 patent and the Andrx product. The '596 patent formulation requires an outer membrane made of something like shellac that is not a polymer. As both Dr. Langer and Paul Maes testified, the shellac coating of Debregeas does not satisfy claim element 1[d]. A3072; A3156. In addition, the shellac coating would prevent the Debregeas formulation from forming an admixture to maintain the solubility in the gastrointestinal tract. The gastrointestinal tract includes the stomach. Because of the enteric shellac membrane that does not dissolve in the stomach, no admixture could possibly form in the stomach, and even if an admixture formed in the lower gastrointestinal tract, it would not "maintain the solubility of Diltiazem throughout the gastrointestinal tract." A3072; A3080–81.

Although the Debregeas patent suggest that one could make equivalent coatings, a coating equivalent to that in Debregeas would (1) not be a polymer and (2) would be enteric. Such a coating would ***not*** permit the sugar at the products core and Diltiazem hydrochloride to form an admixture ***effective to maintain the solubility of Diltiazem*** throughout the gastrointestinal tract. Moreover, the Debregeas patent itself discloses that small changes to the concentrations of substances in the membrane can alter the characteristics of the drug so that it "does not meet the standards of the invention." A14948. Using (as it does) this special enteric, non-polymeric coating, the Debregeas patent does ***not*** disclose a 24-hour, once-a-day formulation.

Thus, Debregeas operates in a substantially different way (with an enteric, non-polymeric coating) to perform a different function (Diltiazem hydrochloride dissolves from the edge inward) with a different result (it lasts eight to twelve hours, and is ***not*** a 24-hour, once-a-day formulation).

These are the same distinctions over Debregeas that the patentees advanced, and on which the examiner relied, in permitting the '791 patent to issue. During the prosecution of the '791 patent, the applicant's explained that in Debregeas the sugar would not dissolve until after the Diltiazem hydrochloride had dissipated and there was no longer any need for a wetting agent to maintain the solubility of Diltiazem. A14520. In his deposition, the inventor Mr. Deboeck

continued to explain that in Debregeas the formulation acts differently and, therefore, that Debregeas does not disclose using sugar as a wetting agent to maintain the solubility of Diltiazem. A16999–7000.

As explained above, the reason for this difference between the '791 patent and '598 patent is primarily the substantial difference in their coating — the non-polymer shellac coating in the '596 patent makes it behave differently. The Andrx product, however, does not use a non-polymer shellac coating like that in the '596 patent. Instead, Andrx uses a coating the same as disclosed in Example 4 of the '791 patent. A3066–67; A3145. Chi Ming Chen, President of Andrx Pharmaceuticals and co-chairman of Andrx Corporation, testified that Andrx tried other coating substances, but ended up copying that used in the '791 patent because the biostudies on the alternatives were unacceptable. A15637–38. When Andrx began working to develop an equivalent to Tiazac®, it tried unsuccessfully to avoid using the same coating used in Tiazac®. *Id.* Because those attempts failed, Andrx switched to using Eudragit NE-30-D as its coating, which is the same principal polymer component as in Tiazac®. *Id.*

Thus, the '596 patent does not exclude the Andrx product from the legitimate scope of equivalents for the '791 patent.

B. THE TRIAL COURT ERRED IN APPLYING PROSECUTION HISTORY ESTOPPEL BECAUSE BIOVAIL DID NOT SURRENDER ITS LEGITIMATE SCOPE OF EQUIVALENTS BY AMENDMENT OR ARGUMENT

The district court also concluded that prosecution history estoppel precluded the '791 patent from reaching the Andrx product under the doctrine of equivalents. A20–22. As this court sitting en banc stated:

> An accused device that does not literally infringe a claim may still infringe under the doctrine of equivalents if each limitation of the claim is met in the accused device either literally or equivalently. Prosecution history estoppel provides a legal limitation on the application of the doctrine of equivalents by excluding from the range of equivalents subject matter surrendered during prosecution of the application for the patent. The estoppel may arise from matter surrendered as a result of amendments to overcome patentability rejections, or as a result of argument to secure allowance of a claim. Prosecution history estoppel is a legal question subject to de novo review on appeal.

Cybor Corp. v. FAS Techs, 138 F.3d 1448, 1459–60, 46 USPQ2d 1169, 1177–78 (Fed. Cir. 1998) (citations omitted).

In evaluating the prosecution history, Courts must determine what was relinquished, and why, to establish the extent of the estoppel. *Merck & Co. v. Mylan Pharmaceuticals, Inc.*, 190 F.3d 1335, 1340, 51 USPQ2d 1954, 1957 (Fed. Cir. 1999). "[E]stoppel is not automatic as to everything beyond the literal scope of the claim; its extent must be determined from what was relinquished, in light of the prior art." *Id.* at 1341. Merely making an argument to the PTO or an amend-

ment to the claims does not raise an absolute estoppel. *Cybor,* 138 F.3d at 1460, 46 USPQ2d at 1178.

In this case, there can be no estoppel. The inventors did not "give up" an interpretation of the claim to a formulation that becomes an admixture in the gastrointestinal tract — the very place where the drug is intended to be used. Nothing in the prosecution history supports any such interpretation. Second, the statements distinguishing the'596 patent do not support that interpretation, since the '596 patent includes layers of shellac which is impenetrable to water. The Andrx product, on the other hand, is completely different. There are no shellac layers in the Andrx beads that prevent water from penetrating to the sugar core, causing it to dissolve, and form an admixture with Diltiazem hydrochloride.

Also, the statements here that the district court held constituted an estoppel were made in a parent application, not in the application that issued as the '791 patent. Of course, "the prosecution history of a parent application may limit the scope of a later application using the same claim term." *Augustine Med., Inc. v. Gaymar Indus.*, 181 F.3d 1291, 1300, 50 USPQ2d 1900, 1907 (Fed. Cir. 1999). However, to be bound by the statement made to the PTO in connection with a later prosecution of a different patent, the statement would have to be one that the examiner relied upon in allowing the claims in the patent at issue. *Georgia-*

Pacific Corp. v. United States Gypsum Co., 195 F.3d 1322, 1333, 52 USPQ2d 1590, 1599 (Fed. Cir. 1999).

In determining whether there has been a clear and unmistakable surrender of subject matter, the prosecution history must be examined as a whole. *See Pharmacia & Upjohn Co. v. Mylan Pharms., Inc.*, 170 F.3d 1373, 1376, 50 USPQ2d 1033, 1036 (Fed. Cir. 1999). An objective standard is applied when looking at the prosecution history, the proper inquiry being "whether a competitor would reasonably believe that the applicant had surrendered the relevant subject matter." *Cybor*, 138 F.3d at 1457, 46 USPQ2d at 1175 (citing *Insituform Techs., Inc. v. Cat Contracting, Inc.*, 99 F.3d 1098, 1107–108, 40 USPQ2d 1602, 1608 (Fed. Cir. 1996)). "The entire record must be analyzed using an objective standard to determine what has been surrendered during prosecution." *Loral Fairchild Corp. v. Sony Corp.*, 181 F.3d 1313, 1327, 50 USPQ2d 1865, 1874 (Fed. Cir. 1999); *Mark I Mktg. Corp. v. R.R. Donnelley & Sons Co.*, 66 F.3d 285, 291, 36 USPQ2d 1095, 1100 (Fed. Cir. 1995) ("The prosecution history must be examined as a whole in determining whether estoppel applies.").

When the prosecution history is examined ***as a whole***, it is clear that statements distinguishing the manufacturing process in the '596 patent were not necessary or even relevant to secure the allowance of the '791 patent, or even its parent. With respect to the inventors' arguments about the differences in the manu-

facturing processes for Debregeas and their invention, the PTO examiner maintained that the manufacturing process "is not critical for composition claims." A14496. Accordingly, the claims were never altered to reflect the manufacturing process. On the other hand, the examiner clearly did recognize the importance of the listed compounds acting as wetting agents when he wrote:

> The composition requires a particular type of wetting agent to be effective. Since it is evident that the release profile of the drug is determined by the particular wetting agents in admixture, the limitations of claim 28 are considered critical and should be incorporated into claim 27 for proper enablement. The wetting agents in contact with the Diltiazem being effective in controlling the solubility of the diltiazem independent of pH.

A3385. When considering the entire application as a whole, a reasonable competitor could only conclude that what is critical is not the manufacturing process or structure, but rather the ***functioning*** of the particular wetting agents in the gastrointestinal tract. There was thus no unmistakable surrender during prosecution of subject matter encompassing the Andrx product.

C. THE RECORD AS A WHOLE COMPELS THE FINDING THAT ANDRX'S PRODUCT IS AT LEAST EQUIVALENT TO THE '791 PATENT.

The doctrine of equivalents is an alternative theory of infringement to literal infringement. Under the doctrine of equivalents, a product or process "that does not literally infringe upon the express terms of a patent claim may nonetheless be found to infringe if there is 'equivalence' between the elements of the ac-

cused product or process and the claimed elements of the patented invention." *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 21 (1997). The central inquiry is whether "the accused product or process contain[s] elements identical or equivalent to each claimed element of the patented invention." Id. at 40. Equivalency is a question of fact. *Id.* at 38.

In order to obtain approval from the FDA for its proposed ANDA for a generic version of Biovail's Tiazac® product (Andrx's ANDA product), Andrx must show that it is bioequivalent to Biovail's Tiazac® product. There is no dispute that Biovail's Tiazac® product is covered by the '791 patent.

Assuming arguendo, that the claims require that the "admixture" be homogeneous, there is no question that the Andrx product is equivalent. The differences between the mixture that forms in the gastrointestinal tract in the Andrx product and a "homogeneous mixture," if one is required, are de minimus, as Dr. Langer testified. A3071–72. That testimony was not refuted by Andrx. Andrx's biostudies for its ANDA demonstrate that the products work in the same way and give the same result. Andrx's experts did not offer any explanation of why Andrx's products function the same as the Tiazac® product, which is covered by the '791 patent. Because Biovail's evidence on this point is uncontested, there are only "insubstantial differences."

The result here sought is defined by the problem to be solved. What was needed was a once-a-day, 24-hour formulation for Diltiazem that would be safe and effective and provide an acceptable dissolution curve. That was the result sought. It is undisputed that the Andrx product produces that result. It is, after all, an ANDA application asserted to be bioequivalent to Biovail's Tiazac®.

The function performed, of maintaining the solubility of Diltiazem, is also beyond dispute. Clearly, the Andrx product must maintain the solubility of Diltiazem in order to obtain the same dissolution test results to establish bioequivalency for its ANDA.

The way in which the '791 patent performs that function to achieve that result is part of what sets it apart from all the prior art Diltiazem delivery systems. That is, the solubility of Diltiazem is maintained (even as it dissociates from Diltiazem hydrochloride in the more neutral pH of the lower gastrointestinal tract) by having it in admixture with one of a number of listed compounds which serve to maintain its solubility — i.e., they act as wetting agents. The presumption of validity, and the attendant presumption of utility, would be enough to establish this point. Here, however, the experimental evidence that sugar does indeed act as a wetting agent is unrefuted. A3155; A14866–67. Neither Dr. Weiner nor Dr. Banakar had any explanation for the test conducted by Mr. Maes that demonstrated that Diltiazem unexpectedly is 55% more soluble in a solution of 16%

sugar. This disbelief by experts is not evidence of non-infringement — it is instead an objective indicia of non-obviousness.

CONCLUSION

For the reasons set forth above, the licensee-manufacturer Biovail and the patentee Galephar respectfully request that the Judgment of the district court be REVERSED and that this case be REMANDED with directions that the district court (i) order that the effective date of any approval of the applicant's Andrx's ANDA be a date not earlier than June 25, 2013, and (ii) enjoin the applicant Andrx from commercially manufacturing, using, offering to sell, selling, or importing into the United States any drug that infringes the '791 patent.

Respectfully Submitted,

Date: May 22, 2000

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PROOF OF SERVICE

Pursuant to Fed. R. App. Proc. 25(c), the undersigned certifies that two copies of the foregoing BRIEF OF PLAINTIFFS-APPELLANTS BIOVAIL CORPORATION INTERNATIONAL, BIOVAIL LABORATORIES, INC., AND GALEPHAR P.R., INC., LTD., were served by deliver to third-party commercial carrier for overnight delivery to:

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On this the 22nd day of May, 2000.

an Attorney for Plaintiffs-Appellants
Biovail Corporation International, Biovail Laboratories, Inc., *and* **Galephar P.R., Inc., Ltd.**

CERTIFICATE OF COMPLIANCE

The undersigned, counsel for Plaintiffs-Appellants Biovail Corporation International, Biovail Laboratories, Inc., and Galephar P.R., Inc., Ltd., certifies pursuant to FED. R. APP. PROC. 32(a)(7)(C) that this foregoing BRIEF OF PLAINTIFFS-APPELLANTS BIOVAIL CORPORATION INTERNATIONAL, BIOVAIL LABORATORIES, INC., AND GALEPHAR P.R., INC., LTD., conforms to the FED. R. APP. PROC. 32(a)(5) and 32(a)(7). Counsel further certifies that according to the word count of the word processing system (Microsoft® Word 97®) used to prepare this brief, the relevant portion of this brief contains 13,519 word.

an Attorney for Plaintiffs-Appellants
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On this the 22nd day of May, 2000.

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Qualified in Queens County
Commission Expires Jan. 31, 2002

an Attorney for Plaintiffs-Appellants
Biovail Corporation International, Biovail Laboratories, Inc., *and* Galephar P.R., Inc., Ltd.

EXHIBIT E

THIS EXHIBIT HAS BEEN REDACTED IN ITS ENTIRETY

EXHIBIT F

THIS EXHIBIT HAS BEEN REDACTED IN ITS ENTIRETY

EXHIBIT 2

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BIOVAIL LABORATORIES INTERNATIONAL SRL, a corporation of Barbados, Plaintiff, v. ANDRX PHARMACEUTICALS, LLC and ANDRX CORPORATION, Defendants.	C.A. Nos. 05-586-KAJ, 05-730-KAJ, and 06-630-KAJ

DECLARATION OF XIU-XIU CHENG

I, Xiu-Xiu Cheng, of Weston, Florida, declare and say as follows:

I am currently employed by Andrx Pharmaceuticals, Inc. (hereinafter "Andrx") having a place of business at 2945 West Corporate Lakes Boulevard, Weston, FL 33331. I have been employed by Andrx since 1995 and have held various positions including Senior Research Scientist, Group Leader in the Research and Development Department, Manager of Product Development, Associate Director of Product Development, and Director of Product Development. My current position is Senior Vice President of Research and Development. During the course of my employment with Andrx, I have been involved with the research, development and manufacture of numerous oral pharmaceutical products, including the product that is the subject of the above-identified lawsuit.

2. I received a Ph.D. in chemical engineering from West Virginia University in 1993 and conducted post doctorate research at West Virginia University School of Pharmacy from 1993 until 1995.

3. During my employment at Andrx, I was involved in Andrx's efforts to develop and market in the United States a generic version of the diltiazem product TIAZAC®. As part of that effort, I was involved in the preparation of an Abbreviated New Drug Application (hereinafter "ANDA") in which Andrx requested permission from the United States Food and Drug Administration (hereinafter the "FDA") to manufacture and sell a generic version of TIAZAC®. The ANDA filed by Andrx with the FDA was assigned ANDA No. 75-401. The product described in ANDA 75-401 is a capsule that is filled with diltiazem HCl extended release pellets.

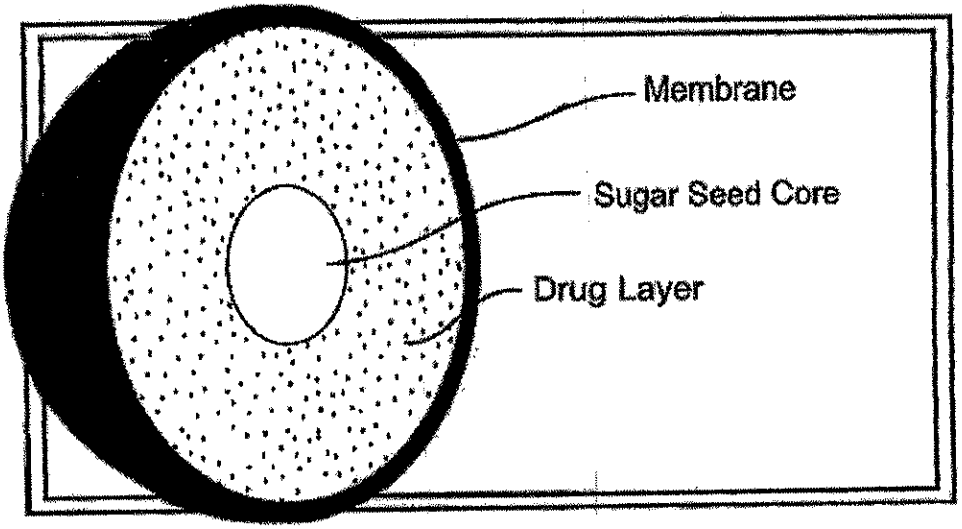
4. ANDA 75-401 contained thousands of pages and described in great detail the ingredients and composition of Andrx's proposed generic version of TIAZAC®. Attached hereto as Exhibit A are a few pages from ANDA 75-401 that summarize the manufacturing procedures, ingredients and components of the diltiazem HCl active pellets in Andrx's generic version of the TIAZAC® product. Attached hereto as Exhibit B are a few pages from ANDA 75-401 that summarize the manufacturing procedures, ingredients and components of the diltiazem HCl extended-release pellets in Andrx's generic version of the TIAZAC® product.

5. During my employment at Andrx, I was involved in Andrx's efforts to develop and market in the United States a generic version of the diltiazem product CARDIZEM LA®. As part of that effort, I was involved in the preparation of an

ANDA in which Andrx requested permission from the FDA to manufacture and sell a generic version of CARDIZEM LA®. The ANDA filed by Andrx with the FDA was assigned ANDA No. 77-686. The product described in ANDA 77-686 is a tablet that is made by compressing diltiazem HCl extended release pellets with other ingredients.

6. ANDA 77-686 contained thousands of pages and described in great detail the ingredients and composition of Andrx's proposed generic version of CARDIZEM LA®. Attached hereto as Exhibit C are a few pages from ANDA 77-686 that summarize the manufacturing procedures, ingredients and components of the diltiazem HCl active pellets in Andrx's generic version of the CARDIZEM LA® product. Attached hereto as Exhibit D are a few pages from ANDA 77-686 that summarize the manufacturing procedures, ingredients and components of the diltiazem HCl extended-release pellets in Andrx's generic version of the CARDIZEM LA® product.

7. The diltiazem HCl extended release pellets used in Andrx's generic versions of the TIAZAC® and CARDIZEM LA® products is a plurality of beads contained in a gelatin capsule. The structure of each of the beads can be represented by the following cross-sectional drawing:



The Andrx beads, as illustrated above, consist of: a) an inert core or sugar sphere; b) a drug layer that is applied to the inert core; and c) an extended release coating or membrane that surrounds the drug layer. The inert core is a sugar sphere. The drug layer is a mixture of [redacted] The extended release coating or membrane contains a mixture of [redacted].

8. The drug layer is applied to the sugar sphere [redacted] and the [redacted] in [redacted] and then dispersing the [redacted] in the [redacted] solution to form a suspension. The suspension is sprayed onto the sugar sphere, and the [redacted] evaporates leaving a mixture of [redacted] layered on the sugar sphere. This spray-coated sugar sphere is referred to as an active pellet. The active pellets are then spray-coated with the extended release coating material.

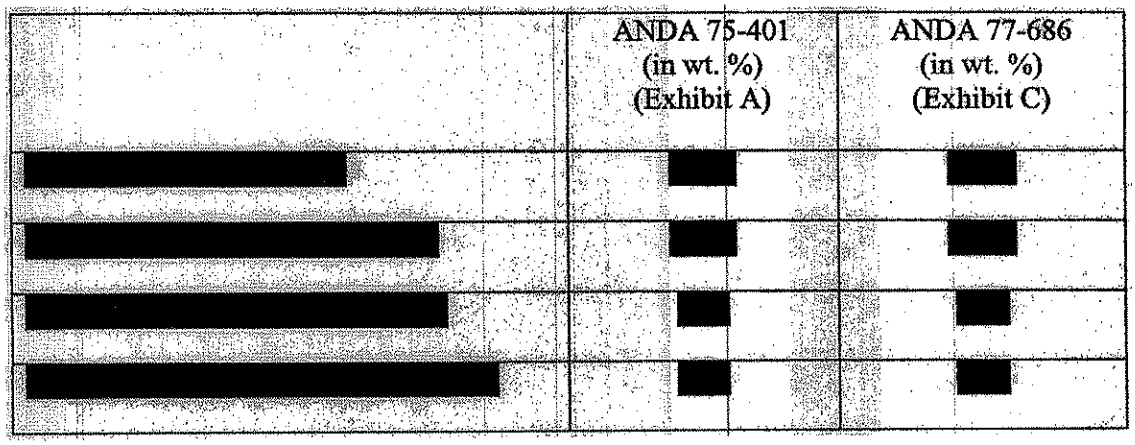
9. [redacted] is a tradename for a compound known as [redacted] or [redacted].

10. [redacted] is the tradename of [redacted] product that is commercially available from Dow Chemical Company.

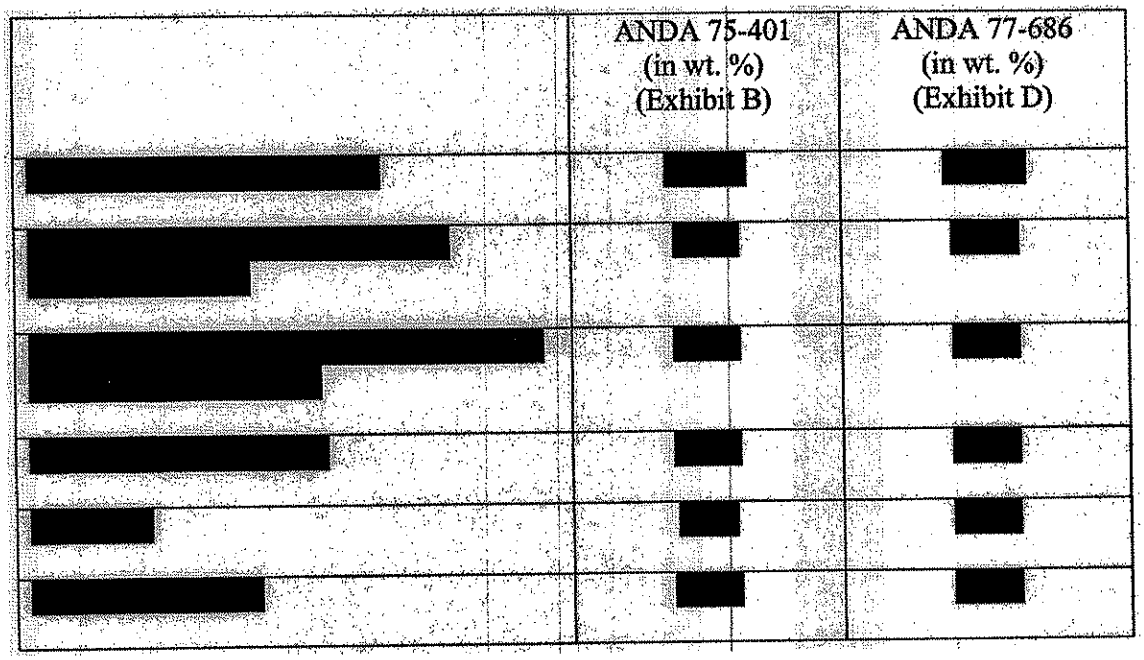
1 I have reviewed sections of both ANDA 75-401 and ANDA 77-686, and I have determined that the composition, ingredients and the percentages of ingredients in both the diltiazem HCl active pellets and the diltiazem HCl extended release pellets in Andrx's generic version of the TIAZAC® product that it sells in the United States under ANDA No. 75-401 are identical to both the diltiazem HCl active pellets and the diltiazem HCl extended release pellets in Andrx's generic version of the CARDIZEM LA® product that it intends to sell in the United States under ANDA 77-686.

12. The amount (as measured in kilograms) of ingredients used in the diltiazem HCl extended release pellets in ANDA 75-401 and ANDA 77-686 is different because the scale of manufacturing has changed, but the percentages and process used to manufacture the extended release pellets in both ANDAs are identical. More specifically, ANDA No. 75-401 described a process for manufacturing approximately [redacted] kg of active pellets and approximately [redacted] kg of extended release pellets and ANDA No. 77-686 describes a process for manufacturing approximately [redacted] kg of active pellets and approximately [redacted] kg of extended release pellets. The amount of active pellets manufactured per batch was [redacted] from ANDA 75-401 to ANDA 77-686. This [redacted] in batch size has no effect on the composition or properties of the extended release pellets.

13. The following table summarizes the composition (by weight percent) of the diltiazem HCl active pellets used in both ANDA 75-401 and ANDA 77-686:



14. Similarly, the following table summarizes the composition (by weight percent) of the diltiazem HCl extended release pellets used in both ANDA 75-401 and ANDA 77-686:



I declare under penalty of perjury that the foregoing is true and correct.

Dated: 11/22/06

Xiu-Xiu Cheng

EXHIBIT A

THIS EXHIBIT HAS BEEN REDACTED IN ITS ENTIRETY

EXHIBIT B

THIS EXHIBIT HAS BEEN REDACTED IN ITS ENTIRETY

EXHIBIT C

THIS EXHIBIT HAS BEEN REDACTED IN ITS ENTIRETY

EXHIBIT D

THIS EXHIBIT HAS BEEN REDACTED IN ITS ENTIRETY